Remarks

Rejection Under 35 U.S.C. § 102

Claims 1 and 8-13 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,075,056 to Quigley *et al.* ("Quigley"). Claims 1-3, 8-13, and 17 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,238,683 to Burnett *et al.* ("Burnett"). Applicants respectfully traverse this rejection.

Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991). A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. (*see Scripps*, 18 USPQ2d at 1010).

In *Air Products*, the district court stated that "a prior art reference which contains a broad general disclosure requiring guessing, testing, speculation or 'picking and choosing' from an encyclopedic disclosure will not anticipate." 219 U.S.P.Q. at 231 (citing *In re Arkley*, 59 C.C.P.A. 804, 455 F.2d 586 (C.C.P.A. 1972)) (in order to anticipate, a piece of prior art "must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing, and combining various disclosures not

directly related to each other by the teachings of the cited reference"); *In re Samour*, 571 F.2d 559, 562 (C.C.P.A. 1972); and *General Battery Corp. v. Gould, Inc.*, 545 F. Supp. 731, 740 (D. Del. 1982)). In *In re Arkley*, 59 C.C.P.A. 804, 455 F.2d 586 (Cust. Pat. App.1972), the Court of Customs and Patent Appeals held that the disclosures of the cited prior art must be sufficiently clear that a person of ordinary skill in the art would understand their full implication without resorting to speculation or guesswork. 455 F.2d at 587.

In *General Battery*, the court noted that a prior art reference "must contain within its four corners, adequate directions for the practice of the patent claim sought to be invalidated." 545 F. Supp. at 744 (internal quotation marks and citation omitted). "Unless all of the same elements are found in exactly the same situation and united in the same way to perform the identical function in a single prior art reference, there is no anticipation." *Id.* (internal quotation marks and citation omitted). In analyzing the prior art reference cited by the defendant, the court found that the references which in combination allegedly anticipate the [patent-in-suit] are scattered throughout the work. One would have to pick and choose among various pages in Vinal to piece together a battery such as that claimed in the patents in suit. This process of selection would require some inventive skills to determine by simply reading Vinal's book that adding sodium sulfate in a conditioning amount to a moist battery would enhance the shelf life of that battery. The elements of the invention are not in the same location nor are adequate directions provided to manufacture the invention.

Analysis

a. Quigley

Quigley describes topical formulations containing an antifungal agent and an anti-inflammatory steroid (abstract). Suitable antifungal agents include benzylamine-containing antifungal agents, such as butenafine, and allylamine-containing antifungal agents, such as terbinafine, naftifine, and the like (col. 2, lines 4-6). Quigley discloses at columns 4 and 5 steroidal anti-inflammatories with potencies between 7 and 1. The potency is dependent not just on the structure of the molecule but also on the manner in which it is formulated (*see* the table at columns 4 and 5).

Quigley discloses generic formulations including a cream (Tables A-C), a gel (Tables D and E), an ointment (Table F), a lotion (Table G), and a liquid formulation (Table H). Examples 1-7 describe the preparation of different bethamethasone dipropionate-containing creams, wherein the concentration is 0.064%. As shown in the table at columns 4 and 5, bethamethasone dipropionate, when formulated in a cream, is a superpotent or potent steroid (classified as category 1 or 2). Examples 8 and 9 describe the preparation of an ointment and gel, respectively, containing bethamethasone dipropionate. Betamethasone dipropionate ointments and gels are generally classified as superpotent or potent steroids (category 1 or 2, *see* the table at cols. 4 and 5).

Betamethasone dipropionate lotions can be classified as lower potency when the concentration is 0.02% (see col. 5, line 30). However, Example 10 describes a lotion containing 0.064% betamethasone dipropionate, which is significantly higher than the concentration in the

table at cols. 4 and 5. The table shows that as the concentration of the steroid increases, the potency of the formulation generally increases. Thus, it is likely that the lotion described in Example 10 would not be classified as low or low-medium potency. Finally, Example 12, which describes the evaluation of the efficacy of various formulations, utilizes betamethasone creams, which are super potent or potent formulations.

In contrast, applicants claim formulations containing a steroidal anti-inflammatory having a potency between 6 and 7 (i.e., low to low-medium potency steroidal anti-inflammatories). This selection of a narrow class of steroidal anti-inflammatories represents less than 20% of what Quigley says is effective. Applicants have presented data which clearly shows the criticality of the small set of steroidal anti-inflammatories specified in the claims and shows unexpected results across this small set (see, for example, the declaration of Dr. Jay Goldstein submitted with the Amendment and Response filed on June 1, 2006 and the Amendment and Response filed on March 14, 2007).

The purpose of Quigley is to provide compositions that have a synergistic effect in that antifungal activity in superior to that shown by the antifungal in the absence of the steroidal anti-inflammatory (col. 2, lines 16-19). Based on Quigley, one would expect to see lower efficacy for the formulations in Quigley when incorporating a low potency steroidal anti-inflammatory, and greater efficacy with stronger steroidal anti-inflammatories. This clearly teaches away from the claimed formulation which specifies that the steroidal anti-inflammatory is has a low to low-medium potency in order to avoid local side effects, such as skin atrophy, striae and

hypopigmentation, and yet has excellent efficacy. This is neither disclosed by nor obvious from Quigley.

Quigley does not disclose or suggest a preference for low to low-medium potency steroids. One of ordinary skill would have to pick and choose among various compounds in various formulations to piece together the claimed formulations. The disclosure in Quigley is not sufficiently clear that a person of ordinary skill in the art would understand their full implication without resorting to speculation or guesswork. Accordingly, claims 1 and 8-13 are novel over Quigley.

b. Burnett

Burnett describes anhydrous compositions for topical delivery of a medicament containing (a) a penetration enhancer/solvent selected from the group consisting of alcohol, propylene glycol, or a combination thereof; (b) a humectant/solvent selected from the group consisting of polyethylene glycol, glycerin, sorbitol, xylitol, or combinations thereof; an anhydrous vehicle; and (d) one or more medicaments (abstract). With respect to Example 1, Burnett alleges that the compositions delivered greater amounts of ketoconazole and desonide to the epidermis and dermis, but less to the receptor versus commercially known formulations such as NIZORAL® and DesOwen® (page 8, paragraph 0036). Burnett alleges that this may clinically translate to lower systemic absorption of the active agents, thereby lowering systemic active agent toxicity (page 8, paragraph 0036).

Burnett requires the use of a penetration enhancer. See abstract, page 3, line 12. There is a description of a formulation that contains in addition to carrier and penetration enhancer 0-2%

ketoconazole and 0-0.05% desonide (see tables 1-4, 7-10). As previously discussed, the carrier can alter the potency of the applied steroidal anti-inflammatory and antifungal. Not only is this an issue when one includes a penetration enhancer, but it causes the steroidal anti-inflammatory to penetrate into the dermis, leading to higher potency of the anti-inflammatory and risking the side effects applicants avoid. This also causes the anti-fungal portion of the composition to be less efficacious at the epidermis, which is the site of the fungal infection.

Referring to applicants' specification, paragraph 3 of the application teaches away from a formulation where the anti-inflammatory penetrates into the dermis: "Steroids can penetrate the skin and cause undesirable side effects, including skin atrophy, hypopigmentation, suppression of the hypothalamic-pituitary-adrenal axis, Cushing's syndrome, and appearance of telangectasias." Paragraph 8 states "The composition can be formulated in any dosage form suitable for topical administration." The result is that one would select a carrier that is topical (i.e., applied to the epidermis) and which does not cause the steroids to penetrate the skin and cause undesirable side effects. This limitation is explicit in the claims.

Therefore, Burnett does not disclose or suggest compositions containing a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation, in a concentration between 0.01 wt% and 5.0 wt%, and having a higher potency than 1 wt% hydrocortisone, and wherein the composition does not cause the steroids to penetrate the skin and cause undesirable local side effects as required by claim 1 and the claims dependent thereon. Accordingly, claims 1-3, 8-13, and 17 are novel over Burnett.

Rejection Under 35 U.S.C. § 103

Claims 2, 3, 7, and 14-17 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Quigley. Claims 4-6 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Burnett in view of U.S. Patent No. 5,219,877 to Shah *et al.* ("Shah"). Applicants respectfully traverse this rejection.

Legal Standard

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459 (1966). This standard was recently affirmed by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). The Court did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

The Supreme Court did not obviate the requirement for the references to provide some motivation to combine as applicants have done, with a reasonable expectation of success. Indeed, the examiner's attention is drawn to the following quote by the Court in *KSR*:

"The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in

the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. . . . There is no necessary inconsistency between the test and the *Graham* analysis."

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

Analysis

1. Quigley

(a) Determining the scope and contents of the prior art

Quigley is discussed above. The Examiner alleges that Quigley teaches desonide cream 0.05% as a suitable anti-inflammatory. The Examiner cites col. 5, line 45 and col. 8, lines 23-24 for support. Col. 5, line 45 is part of the table at cols. 4 and 5 that rates the potency of various steroid formulations. At col. 8, lines 23-24, the specification states that "the steroids suitable for

this invention are described in the Summary of the Invention; preferred is betamethasone dipropionate". There is no mention of desonide. The Summary of the Invention lists suitable steroids; again desonide is not mentioned.

(b) Ascertaining the differences between the prior art and the claims

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983).

The Claimed Compositions

The claims define a topical antifungal composition containing a therapeutically effective amount of an antifungal compound for treating a fungal disease or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation, in a concentration between 0.01 wt% and 5.0 wt%, and having a higher potency than 1 wt% hydrocortisone (i.e., a steroidal anti-inflammatory in the range of 6-7), and a carrier suitable for administration of the antifungal compound and the steroidal anti-inflammatory to the skin, wherein the composition does not cause the steroids to penetrate the skin and cause undesirable local side effects. Quigley's range is 0.001% to 5% steroidal anti-inflammatory (col. 5, line 58), again demonstrating that applicants have selected not only a small number of the steroidal antiinflammatories, but also a subset of the concentration range.

The references alone or in combination do not disclose each and every element of the claims

In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims. As discussed above, Quigley does not disclose or suggest compositions containing a therapeutically effective amount of an antifungal compound for treating a fungal disease or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation as required by the claims. Further, Applicants have presented data which clearly shows the criticality of the small set of steroidal anti-inflammatories specified in the claims and shows unexpected results across this small set (*see* the declaration of Dr. Jay Goldstein submitted with the Amendment and Response filed on June 1, 2006). The Examiner has failed to establish a *prima facie* case of obviousness for at least the reasons discussed above.

The Examiner alleges that Quigley teaches that desonide cream 0.05% is a suitable steroidal anitinflammatory for use in combination with an antifungal. Applicants respectfully disagree. The only mention of desonide in Quigley is in the table at cols. 4 and 5, which is list of various steroidal anti-inflammatories, in various formulations, and their potencies. There is no mention of desonide anywhere else in the description. Thus, there is no teaching or suggestion in Quigley to select desonide. In fact, one of ordinary skill in the art reading Quigley would be motivated to select superpotent or potent betamethasone dipropionate formulations in view of the fact that Quigley explicitly discloses that betamethasone is the preferred drug and the examples

describe the preparation and evaluation of superpotent or potent formulations. Therefore, one of ordinary skill in the art would not be motivated to substitute the desonide of claim 2 for the betamethasone of Quigley as alleged by the Examiner.

The Examiner has failed to establish a *prima facie* case of obviousness for at least the reasons discussed above. Accordingly, claims 2, 3, 7, and 11-14 are not obvious over Quigley.

Quigley teaches away from the claimed compositions

A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicants. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. *In re Caldwell*, 50 C.C.P.A. 1464, 319 F.2d 254, 256, 138 U.S.P.Q. (BNA) 243, 245 (CCPA 1963) (reference teaches away if it leaves the impression that the product would not have the property sought by the applicant).

As discussed above, Quigley describes, in the examples, creams, ointments, and gels containing betamethasone dipropionate. As shown in the table at columns 4 and 5, the formulations described in the examples are classified as high potency or medium-high potency formulations. Example 12 describes the evaluation of betamethasone containing cream, which again is a high potency formulation. One of ordinary skill in the art reading Quigley would be motivated to prepare high or medium-high potency formulations, not the low or low-medium

potency formulations required by the claims, and thus would be lead in a direction divergent from the path Applicants have taken.

2. Burnett in view of Shah

(a) Determining the scope and contents of the prior art

Burnett is discussed above. Shah describes a gel formulation comprising an imidazole antifungal agent, either by itself or in combination with a steroid anti-inflammatory agent. Id., column 3, lines 10-16. A litany of anti-inflammatory steroids is listed at column 3, line 54-column 4, line 2. A preference for mid-potency steroids is expressed at column 4, lines 3-16 of Shah. In fact, Shah discloses that mid-potency steroids are preferred in view of certain disadvantages of strong and low-potency steroids including undesirable side effects such as skin atrophy, rebound phenomenon, and telangiectasia and the fact that low potency steroids may fail to provide fast relief from inflammatory symptoms (col. 4, lines 3-11).

(b) Ascertaining the differences between the prior art and the claims

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983).

The references alone or in combination do not disclose each and every element of the claims

In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims. As discussed above, neither Burnett nor Shah disclose or suggest compositions containing a therapeutically effective amount of an antifungal compound for treating a fungal disease or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation as required by claim 1. Claims 4-6 depend from claim 1. In fact, Shah teaches away from the claimed compositions by disclosing that low to low-medium potency steroidal inflammatories cause undesirable side effects and are not effective in providing relief from inflammation. It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). Accordingly, claims 4-6 are not obvious over Burnett in view of Shah.

Declaration Under 37 CFR 1.132

The Examiner's summary of the declaration under 37 CFR 1.132 filed March 14, 2007 is accurate. However, the Examiner alleges that Quigley discloses a lotion containing betamethasone dipropionate (0.064%), which the Examiner classifies as a low-medium potency steroid. The Examiner cites the excerpt from the Psoriasis Foundation entitled "Potencies of Topical Steroids", which was submitted as Exhibit C with the declaration submitted March 14, 2007. The Examiner has misconstrued Exhibit C and Quigley.

As discussed above, the potency of a steroid is dependent not just on the chemical structure of the steroid, but also on the concentration and the formulation. The table at cols. 4 and 5 in Quigley clearly shows that the potency of betamethasone diproprionate is superpotent or potent in most formulations (e.g., creams, ointments, gels). While the table does show that betamethasone dipropionate lotion is a low-medium potency formulation, this applies where the concentration of betamethasone dipropionate is 0.02% (*see* the table at cols. 4 and 5 of Quigley). The formulation described in exhibit C, which is classified as lower mid strength, contains 0.05% betamethasone dipropionate, which is still lower than the 0.064% described in Quigley. Thus, it is likely that the formulation described in Quigley is a class 3 (upper mid strength) or class 4 (mid strength) based on the teachings of Quigley and the excerpt from the Psoriasis Foundation. In contrast, the claims are limited to low or low-medium potency formulations. Burnett does not disclose or suggest a compositions containing a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation, in a concentration between 0.01 wt% and 5.0 wt%, and having a higher potency than 1 wt% hydrocortisone, as required by claim 1 and the claims dependent thereon.

With regards to the side-by-side comparison, the Examiner alleges that it is unclear why a side-by-side comparison of the claimed compositions with the prior art formulations can not be done. Specifically, the Examiner alleges that the prior art describes formulations containing low to low-medium potency steroids in combination with antifungal compounds. The Examiner has not considered Quigley as a whole. Example 12 in Quigley describes the evaluation of the

efficacy of a cream containing 0.064% betamethasone dipropionate. As shown in the table at cols. 4 and 5 of Quigley, betamethasone diproprionate creams containing 0.05% (which is lower than the concentration in the examples), are classified as super potent or potent formulations. Dr. Goldstein is correct that doing comparative studies with the formulation evaluated in Example 12 in Quigley would have been unethical, since such potent formulations typically cause adverse side effects.

Dr. Goldstein has shown that the compositions used in the examples in the declaration have advantages over other compositions which contain very potent steroids such as betamethasone and dexamethasone (see Goodman and Gilman's The pharmacological Basis of therapeutics, 9th edition, 1996, p1466, attached as exhibit B) associated with severe side effects. It is undesirable to use mid-potency or higher potency steroids for topical treatment for extended periods of time because of associated risks. The compositions exemplified above employ low potency, Class 6 steroids (see attached (Exhibit C) potency chart of steroids listed by the National Psoriasis Foundation), i.e. fluocinalone acetonide, alclometasone dipropionate, desonide, and hydrocortisone 2 ½%, and a carrier which minimizes absorption into the dermis. Other commercialized products have utilized only 1% hydrocortisone, which is too low in potency to have significant anti-inflammatory properties. The claimed compositions utilize prescription strength steroids that are safe for all parts of the skin, are safe for extended periods of use, yet have superior potency as compared to OTC products.

Allowance of claims 1-17 is respectfully solicited.

Respectfully submitted,

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